AMENDMENTS TO THE DRAWINGS:

The attached Appendix A includes two replacement sheets, one for Figures 22 and 23, and one for Figures 24 and 25. The replacement sheets replace original Figures 22 and 23 and Figures 24 and 25 of the above-identified application and have been labeled as "Replacement Sheets." Two annotated sheets providing details of the amendments to Figures 23 and 25 are attached hereto as Appendix B.

Attachments: Appendix A: Replacement Sheets for Figures 22 and 23 and Figures 24 and 25
Appendix B: Annotated Sheet Showing Changes to Figures 23 and 25

REMARKS

Specification

The specification has been amended to correct certain minor editorial errors on page 6 concerning the brief description of Figures 19-25. The brief description of Figure 23 has also been amended to provide a sequence identifier for the cDNA sequence of ErbB3-f12 disclosed in Figure 23.

Applicant submits herewith a substitute sequence listing on a paper form and computer readable form (CRF) to correct certain errors made in the sequence listing submitted on September 10, 2007. In particular, the substitute sequence listing corrects errors in the sequences of SEQ ID NOS:8 and 12-14, and adds information concerning the sequence of SEQ ID NO:17. Support for the amended and new sequences in the substitute sequence listing can be found in the specification as listed in the table below.

SEQ ID NO:	Support
8	Figure 3
12	Page 25, lines 18-19
13	Page 25, lines 21-22
14	Figure 23 (amino acid sequence)
17	Figure 23 (cDNA sequence)

No new matter has been added.

Claims

Claims 1-43 were pending in this application before entry of the amendments made herein. Claims 5 and 15-43 are withdrawn by the Examiner as being drawn to non-elected inventions. Claims 1-4 and 6-14 are currently examined.

Applicant has cancelled claims 1-3, 5, 7, 8 and 15-43 without prejudice to Applicant's right to pursue the subject matter of the cancelled claims in this or other related applications.

Applicant has amended claims 4, 6, 9, 10 and 12-14, and added new claims 44 and 45 for purposes of clarity. In particular, claim 4 has been rewritten in independent form and now recites a method for preventing, treating or delaying neoplasm in a mammal, which method comprises administering to a mammal, to which such prevention, treatment or delay is needed or desirable, an effective amount of an ErbB-3 protein, or a functional fragment thereof, whereby an immune response is generated against said neoplasm is prevented,

treated or delayed, wherein the ErbB-3 protein comprises: (a) the amino acid sequence set forth in SEQ ID NO:1; or (b) at least amino acid residues 24-81 of the amino acid sequence set forth in SEQ ID NO:14; or (c) at least amino acid residues 2-139 of the amino acid sequence set forth in SEQ ID NO:16; or (d) the amino acid sequence set forth in SEQ ID NO:2; or (e) the amino acid sequence set forth in SEQ ID NO:3. Support for amended claim 4 can be found in the specification at, *inter alia*, page 12, lines 5-10; and page 13, lines 5-11.

The dependency of claims 6, 9, 10 and 12-14 have been amended.

New claim 44 has been added to recite that the mammal is a human. Support for new claim 44 can be found in the specification at, *inter alia*, page 12, line 14.

New claim 45 has been added to recite the different routes of administering the ErbB-3 protein or functional fragment thereof to the mammal. Support for new claim 45 can be found in the specification at, *inter alia*, page 16, first paragraph.

No new matter has been added by these amendments. Upon entry of the present amendment, claims 4, 6, 9-14, 44 and 45 will be pending in the present application.

Drawings

Originally filed Figure 23 has been amended to include a sequence identifier for the cDNA sequence of ErbB3-f12 disclosed therein.

Originally filed Figure 25 has been amended to correct an editorial error in the amino acid sequence of SEQ ID NO:16. As is disclosed in the specification (see page 6, line 12), the amino acid sequence set forth in SEQ ID NO:16 corresponds to that of rhErbB3-f78. Amino acid residues 2-139 of the amino acid sequence set forth in SEQ ID NO:16 correspond to a functional fragment of an extracellular domain of the ErbB-3 protein (see specification, *e.g.*, page 4, second paragraph). Specifically, amino acid residues 2-139 of the amino acid sequence set forth in SEQ ID NO:16 correspond to amino acid residues 285-422 of the amino acid sequence of the ErbB-3 protein, SEQ ID NO:1 (see, specification, page 13, lines 5-7). However, amino acid residue 139 of the amino acid sequence set forth in SEQ ID NO:16 was inadvertently omitted from Figure 25. Amino acid residue 139 of the amino acid sequence set forth in SEQ ID NO:16 is "S" (for Serine) and corresponds to amino acid residue 422 of the ErbB-3 protein (see SEQ ID NO:1). Accordingly, Figure 25 has been amended to correct this editorial error.

No new matter has been added by these amendments.

I. THE OBJECTIONS TO THE SPECIFICATION/DRAWINGS SHOULD BE WITHDRAWN

The Examiner objected to Figure 23, because there is no SEQ ID NO identified with the nucleotide sequence disclosed therein. In response, Applicant has amended Figure 23 to insert a sequence identifier (SEQ ID NO:17) for the cDNA sequence of ErbB3-f12. Applicant also has amended the brief description of Figure 23 on page 6 of the specification to reflect this correction. In addition, a substitute sequence listing including the information of SEQ ID NO:17 is submitted herewith.

Therefore, the objection is obviated and should be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-3 and 6-14 are rejected under 35 U.S.C. § 112 ("Section 112"), first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that while the specification discloses that ErbB-3 proteins and fragments in U.S. Patent No. 5,820,859, and those derived from rat ErbB-3, from puffer fish ErbB-3, or from human ErbB-3 can be used, the specification does not disclose any other ErbB-3 proteins, extracellular domains, or functional fragments thereof as broadly encompassed in the claims.

Although Applicant disagrees with the rejection, solely to expedite prosecution of this application, Applicant has cancelled claims 1-3, 7 and 8, and amended the remaining claims to directly or indirectly depend on claim 4, which was not rejected by the Examiner. Therefore, the rejections under Section 112, first paragraph, should be withdrawn.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 1-4, 6, 7, and 9-14 are rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by WO 98/02540 (Genentech, Inc.; Fizpatrick *et al.*) ("Fizpatrick *et al.*"). Specifically, the Examiner alleges that since Fizpatrick *et al.* teaches a method for treating or preventing a neoplasm in a mammal comprising the same claimed step of administering to the mammal the extracellular domain of human ErbB-3, the method taught by Fizpatrick *et al.* would generate an immune response against said neoplasm.

Applicant submits that claims 1-3 and 7 have been cancelled, thereby rendering the rejection moot with respect to these claims.

Applicant also submits that amended claim 4 is not anticipated by Fizpatrick *et al.* for the reasons of below:

First, Fizpatrick *et al.* does not teach administering to a mammal an ErbB-3 protein or a fragment thereof, wherein the ErbB-3 protein comprises (a) the amino acid sequence set forth in SEQ ID NO:1; or (b) at least amino acid residues 24-81 of the amino acid sequence set forth in SEQ ID NO:14; or (c) at least amino acid residues 2-139 of the amino acid sequence set forth in SEQ ID NO:16; or (d) the amino acid sequence set forth in SEQ ID NO:2; or (e) the amino acid sequence set forth in SEQ ID NO:3. Instead, Fizpatrick *et al.* discloses chimeric heteromultimer adhesins that comprise extracellular binding domains of a natural heteromultimer receptor, and bind to the ligand of the natural receptor (see Fizpatrick *et al.*, page 1, lines 3-5). Specifically, Fizpatrick *et al.* discloses chimeric heteromultimer adhesins that comprises extracellular domains of a pair of monomers of the natural receptor ErbB2/ErbB3 and ErbB2/ErbB4 (see Fizpatrick *et al.*, page 8, lines 8-11). Fizpatrick *et al.* further discloses that the chimeric heteromultimer adhesins can either be a chimeric heterodimer immunoadhesin, such as ErbB2/3-IgG, ErbB2/4-IgG, or ErbB3/4-IgG, or a chimeric homodimer immunoadhesin, such as ErbB2/2-IgG, ErbB3/3-IgG, or ErbB4/4-IgG (see Fizpatrick *et al.*, Figure 1). However, Fizpatrick *et al.* does not teach that the chimeric heteromultimer adhesins can be only a monomer of an ErbB (*i.e.*, an ErbB-3 protein or a functional fragment thereof), much less an ErbB-3 protein (or functional fragment thereof) comprising (a) the amino acid sequence set forth in SEQ ID NO:1; or (b) at least amino acid residues 24-81 of the amino acid sequence set forth in SEQ ID NO:14; or (c) at least amino acid residues 2-139 of the amino acid sequence set forth in SEQ ID NO:16; or (d) the amino acid sequence set forth in SEQ ID NO:2; or (e) the amino acid sequence set forth in SEQ ID NO:3, as recited in amended claim 4. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

In addition, the method taught by Fizpatrick *et al.* does <u>not</u> generate the immune response recited in amended claim 4, since the chimeric heteromultimer adhesins administered by Fizpatrick *et al.* is structurally and functionally different from the ErbB-3 protein (or functional fragment thereof) used in the claimed method.

For at least the foregoing reasons, amended claim 4 and its dependent claims are not anticipated by Fizpatrick *et al.* Therefore, withdrawal of the Section 102(b) rejections is respectfully requested.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1, 7, and 8 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being unpatentable over Fizpatrick *et al.* The Examiner acknowledges that Fizpatrick *et al.* does not teach administration of the ErbB-3 protein or immune response potentiator to the neoplasm *in situ.* However, the Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the ErbB-3 protein or immune response potentiator to the neoplasm because Fizpatrick *et al.* teach that the route of administration may be modified to obtain a maximum therapeutic effect and treatment at the site where excessive levels of heregulin ligand are present or excess activation of receptors by heregulin is occurring in the mammal, such as cancer, is desirable. The Examiner also alleges that one would have been motivated to administer the ErbB-3 protein or immune response potentiator to the neoplasm in order to treat the neoplasm, and that one of ordinary skill in the art would have a reasonable expectation of success administering the ErbB-3 protein or immune response potentiator to the neoplasm because methods of administering proteins to or in the vicinity of a neoplasm are known and successful in the art.

As a preliminary matter, Applicant submits that claims 1, 7 and 8 have been cancelled, thereby rendering the rejection moot.

For the following reasons, Applicant submits that amended claim 4 and its dependent claims are not obvious over Fizpatrick *et al.*

1. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court rejected a rigid application of the "teaching, suggestion, or

motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739, 82 U.S.P.Q.2d at 1395. However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S. Ct. at 1741, 82 U.S.P.Q.2d at 1396.

A *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

With regard to the final point, the Supreme Court in *KSR* citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S. Ct. at 1742, 82 U.S.P.Q.2d at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S. Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A. 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* – which are still good law post-*KSR* – require that *both* the suggestion and the expectation of success must be found in the prior art, and not from knowledge gained from the Applicant's disclosure.

2. The Claims Are Not Obvious Over Fizpatrick *et al.*

As discussed above, Fizpatrick *et al.* discloses chimeric multimer immunoadhesins, which are homodimers or heterodimers that consists of pairs of monomers of ErbB2, ErbB3, ErbB4, or any combination thereof, and an immunoglobulin constant region such as IgG (see Figure 1). Fizpatrick *et al.* does not teach or suggest using an ErbB monomer, much less teach or suggest an ErbB3 protein comprising the amino acid sequences or residues recited in

amended claim 4. A person of ordinary skill in the art would find no reason to modify the teaching of Fizpatrick *et al.* to use an ErbB3 monomer, since such modification would be contrary to the teaching of Fizpatrick *et al.* In particular, Fizpatrick *et al.* discloses that the chimeric heteromultimer adhesins is an antagonist of the ligand that binds to the extracellular domain of a monomer of the natural heteromultimeric receptor, and are useful in treating disease states resulting from ligand binding and activation of the natural receptor (see Fizpatrick *et al.*, page 1, lines 3-5; page 5, lines 24-25; page 10, lines 4-7; page 16, lines 29-31; and page 23, lines 25-29). Essentially, Fizpatrick *et al.*'s chimeric heteromultimer adhesins mimic the natural receptor and competitively bind the ligand of the natural receptor and prevent receptor activation by reducing excess levels of the ligand (see Fizpatrick *et al.*, page 16, lines 29-31; and page 25, lines 1-3). The person of ordinary skill in the art would understand that a monomer is structurally different from the heteromultimeric natural receptor (*i.e.*, the latter comprising more than one monomers, the presence of which would induce change in conformation and creation of binding site(s)), and that a monomer could not bind the ligand of the natural receptor, and thus, could not be the chimeric heteromultimer adhesin of Fizpatrick *et al.*

Moreover, Fizpatrick *et al.* shows that amongst the various homodimers and heterodimers tested for ligand binding affinity, ErbB2/3-IgG and ErbB2/4-IgG heterodimer immunoadhesins exhibited the highest affinity for the ligand heregulin (HRG) (see Fizpatrick *et al.*, Table 1 at page 38; and page 38, lines 27-30). Specifically, Fizpatrick *et al.* teaches that ErbB2/3-IgG and ErbB2/4-IgG heterodimers are better than ErbB3/3-IgG and ErbB4/4-IgG homodimers, and are better than ErbB3/4-IgG heterodimers at binding heregulin, and speculated that this is due to physical interaction of the extracellular domain of ErbB2 with the extracellular domain of either ErbB3 or ErbB4 which results in the formation of a high affinity growth factor binding site (see page 38, lines 10-12; and page 38, line 30 to page 39, line 4). Thus, Fizpatrick *et al.* shows that the extracellular domain of ErbB2 modulates the binding of heregulin to ErbB3 and ErbB4, and postulates that under normal biological conditions, "ErbB2's sole function appears to be to mediate HRG and EGF ligand responses as a common member of these receptor complexes" (see Fizpatrick *et al.*, page 38, line 23; and page 40, lines 30-31). At most, Fizpatrick suggests the use of a multimer adhesin comprising at least one ErbB2 monomer dimerized with another ErbB monomer. There is no teaching or suggestion in Fizpatrick *et al.* to use any ErbB monomer without an ErbB2 monomer. Indeed, Fizpatrick *et al.* teaches away from the use of monomers because ErbB

monomers exhibit significantly reduced affinity for ligand, when compared to soluble chimeric heteromultimer adhesins (see Fizpatrick *et al.*, page 5, lines 21-22).

Furthermore, there is no reasonable expectation of success to use an ErbB-3 protein or a functional fragment thereof, based on the teaching of Fizpatrick *et al.*, because Fizpatrick *et al.*'s chimeric heteromultimer adhesins have different mechanism of actions than the ErbB-3 protein (or functional fragment thereof) of the claimed methods. In Fizpatrick *et al.*, the chimeric multimeric adhesins are used as a high affinity soluble receptor complex that act as antagonists to treat the condition where excessive levels of neuregulin are present and where excessive activation of ErbB receptors by neuregulin ligand is occurring (see Fizpatrick *et al.*, page 5, lines 24-25; page 25, lines 1-3; and page 39, lines 8-10). The multimeric adhesins of Fizpatrick *et al.* do not generate an immune response, much less generate an immune response against a neoplasm. The chimeric heteromultimer adhesins disclosed in all the examples of Fizpatrick *et al.* are immmunoadhesins, which combine the binding domain of a protein, such as an extracellular domain of an ErbB protein, with an immunoglobulin constant domain (see Fizpatrick *et al.*, page 12, lines 11-13; and page 35 line 19 to page 36, line 2). According to Fizpatrick *et al.*, "[s]uch immunoadhesins are *minimally* immunogenic to the patient" (see page 12, line 17) (emphasis added). By contrast, the administered ErbB-3 monomer (or functional fragment thereof) is intended to be immunogenic and to elicit an immune response against a neoplasm in order to prevent, treat, or delay the neoplasm. In other words, the presently claimed invention discloses a vaccine, wherein an ErbB-3 protein or functional fragment thereof acts as an antigen to induce a specific immune response against that antigen, *i.e.*, against the ErbB-3 protein or functional fragment thereof (see specification, page 23, lines 11-14). On the other hand, the chimeric heteromultimer adhesins of Fizpatrick *et al.* physically associate with the ligand and prevent the ligand from binding to the natural receptor, whereas the ErbB-3 protein (or functional fragment thereof) does not associate with the ligand. Because the ErbB-3 protein (or functional fragment thereof) functions differently than the chimeric heteromultimer adhesins of Fizpatrick *et al.*, there is no reasonable expectation of success to use the chimeric heteromultimer adhesins of Fizpatrick *et al.* to arrive at the claimed method.

For at least the foregoing reasons, Applicant submits that amended claim 4 and its dependent claims are not obvious over Fizpatrick *et al.* Withdrawal of the Section 103(a) rejections is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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For: Anthony C. Chen (Reg. No. 38,673)
By: Eric G. Lee (Reg. No. 59,746)
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

Enclosures